

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 1-23, 25 and 29 are currently pending in the application, with claims 1 and 23 being the independent claims. No claim is amended.

II. Priority

The Office Action, at page 2, requests submission of a certified copy of the priority European application.

A request to obtain a copy of the priority document has been submitted to the European Patent Office. Applicants will submit a certified copy of the priority document as soon as it becomes available.

III. The Rejections Under 35 U.S.C. § 103(a)

A. The Rejection over Lee

The Office Action, at pages 2-5, rejects claims 1, 5-13, 15 and 20-22 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee"). Applicants respectfully traverse this ground of rejection.

1. The Claimed Invention

The presently claimed invention is directed to a method for analyzing the metabolites of a biological sample, which comprises quantitatively determining one or more metabolites in the sample in a way that the quantitative determination resolves isotopic mass differences within one metabolite, wherein the sample comprises or is derived from a cell which has been maintained

under conditions which allow the uptake of an isotopically-labeled metabolizable compound so that the metabolites in the cell are saturated with the isotope with which the metabolizable compound is labeled.

Further, the claimed invention is drawn to isotopically-labeled metabolites obtainable from such a sample.

2. The Cited Prior Art Fails to Teach or Suggest Each and Every Element of the Claimed Invention

Lee discloses metabolic flux studies. In fact, the Abstract of Lee clearly teaches the following:

The method involves the application of a technology which makes it possible to determine *metabolic processes involved in the formation of any glucose-based metabolite*. A precursor molecule is labelled with a stable carbon (^{13}C) isotope at specific positions. The label is allowed to distribute and rearrange in the system. Metabolites are recovered and analyzed against a control system or known biochemical reactions and/or cycles to determine information such as *metabolic pathway substrate flux* caused by a compound acting on the system.

(emphasis added)

Flux studies generally involve the measurement of a certain set of metabolites in a given biological system and correlating the collected data to models for metabolic pathways. This is, for example, referred to as "Dynamic ^{13}C flow measurements". See Figure 1 in Lee.

There is a qualitative difference between metabolic flux studies and metabolic profiling according to the present invention. The former technique, namely metabolic flux studies, requires a partial labeling of the metabolites because flux studies require changes of the degree of labeling. Flux studies monitor the kinetics of stable isotope enrichment through analysis of mass isotopomer distributions. The information is normally collected at different times during the process, before a saturation occurs. In contrast to partial flux labeling, full labeling of the metabolites represents an endpoint, which does not reveal kinetic properties.

The present invention provides a complete labeling, such that fully labeled metabolites are obtained and compared with metabolites of a second biological sample. This is described in the present application as follows:

However, flux studies differ from the method of the invention in that they generally involve partial labeling of the metabolites of a cell. This is explained by the fact that flux studies require partial, i.e. incomplete, labeling. By contrast, the method of the present invention achieves saturating labeling which means a labeling of the metabolites as complete as possible given the degree of labeling in the isotopically labeled metabolizable compound used to label the cell from which the biological sample for analyses is derived.

Specification at page 5, first paragraph. Further, the specification, at page 10, defines the term "saturated" as follows:

It is a critical feature of the method of the invention that the metabolites are saturated with the isotopic labeling. "Saturated" (or "saturating labeling") means that the metabolites in the cell or the biological sample derived therefrom contain an amount of isotope label that substantially corresponds to the amount of label in the metabolize compound taken up by the cell in order to label it, and that substantially all of the metabolites to be analyzed contain the isotope label.

Thus, the specification clearly teaches a complete isotopic labeling. Therefore, the artisan skilled in the art would understand from the specification that the "amount of isotope label in the metabolizable compound taken up by the cell in order to label it" as mentioned in the present application refers to the compound that is actually labeled and must not include unlabeled versions of the same compound.

Furthermore, with regard to the precursor molecule, Lee emphasizes precise labeling on specific known positions of the precursor molecule or "smart" labeling, so that metabolization and propagation of ^{13}C on metabolites can be precisely determined (*see* paragraph [0028]).

Contrary to Lee, the method claimed in the present application requires saturated labeling of the metabolites.

Thus, Lee fails to teach or suggest a method wherein the metabolites are saturated with the isotope labeling. Accordingly, Lee fails to disclose or suggest the claimed invention.

2. There is no Reason to combine the Elements in the Fashion Claimed

The Office Action, at page 3, contends that it would have been obvious to one of ordinary skill in the art from the teachings of Lee to use a sampling of labeled cells after a time consistent with saturation of metabolites with labeled isotope.

The Office's allegation, however, is impermissible. In fact, a saturated labeling would make no sense in the method of Lee since this would lead to a homogenous distribution of the ¹³C label in all the metabolites and on all positions, rather than partial labeling and only on specific positions. Thus, it wouldn't be possible to detect influences of drugs or substances on the metabolism as intended by the method of Lee.

Thus, at least for the reasons stated above, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

B. The Rejection over Lee in view of Abramson

The Office Action, at pages 5-6, rejects claims 2-4 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* ("Lee") in view of US Patent Application Publication No. 2003/0077572 A1 to Abramson *et al.* ("Abramson"). Applicants respectfully traverse this ground of rejection.

Abramson does not remedy the deficiencies of Lee described above. In fact, Abramson discloses differential labeling of two cell populations, each labeled to a different extent. Thus, Abramson fails to teach or suggest saturated labeling.

Accordingly, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

C. The Rejection Over Lee in view of Kasper

The Office Action, at pages 6-7, rejects claim 14 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* (“Lee”) in view of US Patent Application Publication No. 2005/0112706 A1 to Kasper. Applicants respectfully traverse this ground of rejection.

Kasper discloses methods for determining androgen responsiveness in a sample using bioassays. Kasper fails to teach or suggest cell labeling, let alone saturated labeling. Thus, Kasper fails to remedy the deficiencies of Lee.

Accordingly, the rejection is improper and should be withdrawn.

D. The Rejection Over Lee in view of Birkemeyer

The Office Action, at pages 7-8, rejects claims 16-17 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* (“Lee”) in view of Birkemeyer *et al.* 2003 J. Chromatography A 993: 89 (“Birkemeyer”). Applicants respectfully traverse this ground of rejection.

Birkemeyer discloses gas chromatography analysis of phytohormones. The reference fails to teach or suggest isotope labeling, let alone saturated labeling, and thus fails to remedy the deficiencies of Lee described above.

Thus, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

E. The Rejection Over Lee in view of Hellerstein-APEM

The Office Action, at pages 8-9, rejects claims 18-19 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* (“Lee”) in view of MK Hellerstein and RA Neese 1999 *American J. Physiol. Endocr. Metab.* 276: 1146- 1170 (“Hellerstein-APEM”). Applicants respectfully traverse this ground of rejection.

Hellerstein-APEM fails to remedy the deficiencies of Lee described above, as the reference provides a review of mass isotopomer distribution. Accordingly, the rejection is improper and should be withdrawn.

F. The Rejection Over Lee in view of Hellerstein

The Office Action, at page 9, rejects claim 25 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* (“Lee”) in view of US Patent Application Publication No. 2004/00811994 A1 to Hellerstein (“Hellerstein”). Applicants respectfully traverse this ground of rejection.

Hellerstein discloses biochemical methods for assessing metabolic fitness. The reference fails to teach or suggest cell labeling, and thus fails to remedy the deficiencies of Lee described above. Accordingly, the rejection is improper and should be withdrawn.

G. The Rejection Over Lee in view of Evans

The Office Action, at pages 9-10, rejects claim 23 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* (“Lee”) in view of US Patent No. 5,532,206 to Evans *et al.* (“Evans”). Applicants respectfully traverse this ground of rejection.

Evans does not remedy the deficiencies of Lee described above as the patent discloses application of ¹⁶C- or ¹⁷C-gibberellin to plants.

Accordingly, the rejection is improper and should be withdrawn.

H. The Rejection Over Lee in view of Evans and Further in view of Hellerstein

The Office Action, at page 10, rejects claim 29 under 35 U.S.C. § 103(a) as allegedly being obvious over US Patent Application Publication No. 2003/0180710 A1 to Lee *et al.* (“Lee”) in view of US Patent No. 5,532,206 to Evans *et al.* (“Evans”) and further in view of US Patent Application Publication No. 2004/00811994 A1 to Hellerstein (“Hellerstein”). Applicants respectfully traverse this ground of rejection.

As discussed above, none of the cited references teaches or suggest the claimed invention. Thus, the rejection is improper.

Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date June 22, 2009

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5527
Facsimile: (202) 672-5399

By Liliana Di Nola-Baron

for Liliana Di Nola-Baron
Agent for Applicants
Registration No. 56,073